Leukemia

Major finding: NOTCH-regulated long noncoding RNAs (lncRNA) including *LUNAR1* promote T-ALL cell growth.

Mechanism: *LUNAR1* enhances T-ALL growth via *cis* activation of *IGF1R* expression and IGF1 signaling.

Impact: lncRNAs regulate tumor maintenance and may serve as biomarkers or therapeutic targets.

GENOME-WIDE MAPPING IDENTIFIES T-ALL–SPECIFIC NOTCH-REGULATED lncRNAs

Malignant transformation of T-lymphocyte progenitors results in T-cell acute lymphoblastic leukemia (T-ALL), an aggressive disease that is frequently associated with activating mutations in *NOTCH1* and exhibits a high mortality rate. Although genetic and epigenetic changes and the role of microRNAs have been characterized in T-ALL, the contribution of long noncoding RNAs (lncRNA), which lack protein-coding potential but may enhance the expression of neighboring genes, has yet to be studied. Trimarchi and colleagues combined ultra–high-depth RNA-sequencing and genome-wide chromatin state mapping to generate an all-inclusive lncRNA expression map in T-ALL. This analysis demonstrated tissue-specific expression of lncRNAs in T-ALL and normal T cells and identified previously uncharacterized T-ALL–specific lncRNAs. Additionally, examination of lncRNA promoters revealed enrichment of the NOTCH1/recombination signal binding protein for immunoglobulin κ J region (RBPJκ) transcriptional activator complex, suggesting that oncogenic NOTCH signaling may directly regulate the expression of a subset of lncRNAs. Indeed, NOTCH1 inhibition identified a NOTCH-dependent T-ALL lncRNA expression program that was differentially expressed in primary human *NOTCH1*-mutant T-ALLs compared with normal T cells. Leukemia-induced noncoding activator RNA 1 (*LUNAR1*), a NOTCH-regulated lncRNA, was highly expressed in T-ALL, in particular in T-ALL samples harboring *NOTCH1* mutations, and was downregulated in response to NOTCH inhibition. *LUNAR1* expression was regulated by an active NOTCH1-occupied enhancer in the nearby insulin-like growth factor1 receptor (*IGF1R*) gene. Furthermore, depletion of *LUNAR1* reduced expression of *IGF1R* and IGF1 signaling and diminished T-ALL tumor growth. *LUNAR1* functioned as an important component of the *IGF1R* enhancer and activated *IGF1R* expression in *cis* by recruiting the Mediator complex and RNA polymerase II to the *IGF1R* enhancer. These results identify *LUNAR1* as a positive regulator of T-ALL cell growth and suggest lncRNAs as potential therapeutic targets for leukemia. ■

Trimarchi T, Bilal E, Ntziachristos P, Fabbri G, Dalla-Favera R, Tsirigos A, et al. Genome-wide mapping and characterization of NOTCH-regulated long noncoding RNAs in acute leukemia. Cell 2014;158:593–606.

Epigenetics

Major finding: Homozygous loss of *SUZ12* or *EED* is prevalent in NF1-associated malignancies.

Mechanism: Reduced H3K27me3 and increased H3K27Ac caused by *SUZ12* loss confer sensitivity to BRD4 inhibition.

Impact: Combined BRD4 and MEK inhibition may suppress RAS transcriptional output in *NF1*-deficient tumors.

PRC2 SUBUNITS ARE TUMOR SUPPRESSORS IN *NF1*-DEFICIENT SOLID TUMORS

Genetic loss of neurofibromin 1 (*NF1*) underlies neurofibromatosis type 1, a familial cancer predisposition syndrome characterized by the growth of nervous system tumors. Patients harboring a germline 17q microdeletion causing the loss of *NF1* and 13 other genes have a dramatic increase in the number of benign neurofibromas and a much higher incidence of malignant peripheral nerve sheath tumors (MPNST), suggesting that a cooperating tumor suppressor lies within this region. De Raedt, Beert, Pasmant, and colleagues performed comparative genomic hybridization on 51 *NF1*-deficient MPNSTs and found heterozygous or homozygous deletions or mutations of *SUZ12*, a gene within the microdeletion region that encodes a Polycomb repressive complex 2 (PRC2) subunit, in both microdeletion and non-microdeletion MPNSTs. Notably, another PRC2 gene, *EED*, was recurrently deleted or mutated in MPNSTs, further implicating PRC2 inactivation in MPNST development. Consistent with these findings, reexpression of SUZ12 suppressed the growth of *NF1*-deficient but not *NF1*–wild-type tumor cells, and deletion of *Suz12* in *cis* with *Nf1* accelerated tumor formation and decreased survival in mice. Given that loss of H3K27 trimethylation caused by PRC2 inactivation can increase H3K27 acetylation, which recruits bromodomain proteins like BRD4, the authors hypothesized that *SUZ12* loss might confer sensitivity to bromodomain inhibitors. Indeed, *SUZ12*-mutant MPNST cells were more sensitive to JQ1 than *SUZ12*–wild-type cells. However, JQ1 had only cytostatic effects in *SUZ12*-mutant MPNST cells, whereas the combination of JQ1 and a MEK inhibitor was cytotoxic and induced significant tumor regression *in vivo*. JQ1 suppressed RAS-driven transcription in part by displacing BRD4 from RAS signature genes, but JQ1 and the MEK inhibitor suppressed RAS signature gene expression more potently together than either agent alone. In addition to identifying an epigenetically driven link between PRC2 and RAS in the development of *NF1*-deficient tumors, these findings provide a rationale for evaluation of BRD4 and MEK inhibitor combination therapy in patients with *NF1*-deficient tumors. ■

De Raedt T, Beert E, Pasmant E, Luscan A, Brems H, Ortonne N, et al. PRC2 loss amplifies Ras-driven transcription and confers sensitivity to BRD4-based therapies. Nature 2014 Aug 13 [Epub ahead of print].

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